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09/694,758	10/23/2000	Shukti Chakravarti	CWV-001.01	7408

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EXAMINER
PONNALURI, PADMASHRI

ART UNIT	PAPER NUMBER
1627	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/694,758	Applicant(s) Chakravarti
	Examiner Padmashri Ponnaluri	Art Unit 1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 16, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *5-7* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *5-7* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This application claims priority to a provisional application 60/160,835.

2. Claims 5-7 are currently pending in this application.

3. Claims 1-4 and 8-18 have been canceled by the amendment filed on 5/16/02.

4. Applicant's election with traverse of group IV, claims 5-7, and MMP-12 (as species of gene used in the method) in Paper No. 9, filed on 5/16/02 is acknowledged. The traversal is on the ground(s) that claims 1-4 have been improperly restricted into 3 separate invention, applicants submit that claims 1-4 are directed to the same invention, and therefore should be grouped as a single invention. This is not found persuasive because claim 1 method is drawn to a method for identifying genes; and claim 3 method is drawn to generating nucleic acid probes, which can be used in claim 1 method; and claim 4 method is drawn to a method of generating a kit, which is different from the method of claim 1. Thus, restriction between the groups is proper.

Applicants further argue the restriction between claims 13 and 17. Applicants arguments are not persuasive, because claim 13 is drawn to a method of treating a patient, however the claim does not recite how the patient is treated; and claim 17 is drawn to a method of treating an animal by administering the compound identified in claim 16. Thus, both claim 13 and claim 17 methods are different from each other.

The requirement is still deemed proper and is therefore made FINAL.

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CAR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the citizenship of the inventor. The inventors' the country of citizenship has to be included in the Oath/declaration.

6. The disclosure is objected to because of the following informalities:

a) the specification refers to table 1, however table 1 is not found in the specification. If applicants mean the 'X exemplification' as table 1, applicants are requested to label the table.

b) the specification in page 46, recites "SEQ ID Nos: 1-146", but the sequences are no where found in the case.

Appropriate correction is required.

7. Claim 5 is objected to because of the following informalities: claim 5 is dependent on the canceled claim 1. Appropriate correction is required.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 5-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method for determining the phenotype of a cell, comprising detecting the differential expression relative to normal cell of at least one gene shown in table 1, or other IBD genes identified according to the method of claim 1.

The specification description is directed to a method for identification of genes which are up or down regulated in intestinal tissue of patients by comparing with the genes expressed by intestinal tissue of healthy people, and thus identified genes are used in the method of the instant claim method. Thus the genes involved in the IBD genes have to be identified in a screening assay , and the identified genes are used in the claimed assay.

The specification disclosure does not recite or has given examples of the identified IBD genes which can be used in the instant method. The specification in pages 41 and further disclose the diagnostic and prognostic assays. In this section, the specification discusses that 'by detecting the disclosed biomarkers, i.e., the disclosed nucleic acid markers (see table 1) and/or polypeptide markers for IBD encoded thereby. However, table 1, recites grouping of known genes which may have a role in IBD. The specification table 1, does not include any gene sequences, as disclosed in the specification. The specification disclosure is narrative and does not include any working examples of experiments in which the genes involved in up- pr down-regulated genes in intestinal tissue of patients are used in the method of determining phenotype or to assess a

patient's risk of having or developing an inflammatory bowel disease. Thus, applicants are not in possession of the genes involved in the IBD.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Thus, it requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s).

In the present instance, the claimed invention contains no identifying characteristics regarding the IBD genes identified by the method of claim 1.

Additionally, the narrow scope of examples directed to specific genes are clearly not representative of the scope of combinatorial library compounds of the presently claimed invention.

10.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the instant claimed method does not recite how or which phenotype of the cell is determined; and the relationship of phenotype and the patients risk of having IBD.

Claim 5 is vague and indefinite by reciting ' phenotype of a cell', it is not clear what does applicants mean by phenotype of a cell. Does applicants mean that physical changes of a cell or the method uses external markers, etc., it is not clear. Applicants are requested to clarify.

Claim 5 is vague and indefinite by reciting ' particularly intestinal origin'; and does applicants mean 'intestinal tissue cell of a patient having IBD'. Applicants are requested to clarify.

Claim 5 recites that 'relative to normal cell', does applicants mean any normal cell or intestinal tissue cell. Applicants are requested to clarify.

Claim 6 recites the limitation "the assay" in line 1. There is insufficient antecedent basis for this limitation in the claim.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Puolakkaiene et al (Gastroenterrology, vol. 114, No. 4, April 15, 1998 page A1064).

The instant claims recite a method for determining phenotype of a intestinal cell of comprising detecting the differential expression of MMP-12 (macrophage elastase) or other IBD genes relative to normal cell.

Puolakkainen et al disclose distinct expression profiles of Stromelysin-2 (MMP-10), collagenase-3 (MMP-13), macrophage metalloelastase (HME, MMP-12) (refers to the elected gene in table 1) and TIMP-3 in intestinal ulcerations. The reference discloses that to define the role of matrix degrading enzymes and their inhibitors in intestinal inflammation and ulcerations, the expression of (refers to the differential expression of the instant claims) Stromelysin-2 (MMP-10), collagenase-3 (MMP-13), macrophage metalloelastase (HME, MMP-12) and TIMP-3 was studied using 38 samples representing ulcerative colitis, Crohn's disease, ischemic colitis (i.e., inflammatory bowel diseases), and normal intestine. The reference discloses that MMP-12 (HME) was abundantly expressed by macrophage in the vicinity of shedding mucosal epithelium and beneath the nercotic surface of the ulcers. The reference clearly anticipates the claimed invention.

14. Claims 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexander et al (Digestive Diseases and Sciences, vol. 41, No. 4, April 1996, pp 660-669) (reference provided by applicants in PTO 1449, filed on 5/16/02).

Alexander et al disclose a method into determine altered expression of protooncogenes (cell cycle related genes) in patients with inflammatory bowel disease (IBD). The reference assayed transcripts of 15 protooncogenes (refer to other IBD genes of the instant claims) in colonic epithelial cells of IBD patients and controls (see abstract). The reference discloses that increased levels of soluble mediators (e.g. Leukotrienes, prostaglandins) (refer to other IBD genes of the instant claims) of inflammation as well of the cells of immune system have been found to be present in the intestinal mucosa and submucosa of IBD patients (see page 660, last paragraph bridging first paragraph in page 661). The reference discloses expression of transcripts of eight growth factor receptor related genes in colonic epithelial cells of IBD patients and controls (see left column in page 661). The reference discloses that increased expression of PDGF-R-β mRNA involved epithelium, compared to matched uninvolved epithelium, and the transcript level of this gene, as well three other growth factors was considerably higher in colonic epithelial cells of IBD patients (see page 661).

The reference discloses that prior to determining whether there were any differences between IBD samples and controls in their relative expression of protooncogene transcripts, it was necessary to determine the degree of expression of each of the genes in normal colon epithelial cells (see page 662, right column, section under results). The reference discloses that

hybridization of radio labeled probes to slot blots of RNA extracted from normal epithelial cells of patients rejected for diverticulitis and sporadic cancer revealed that transcripts of five protooncogenes were abundant in these samples (refers to a method of selecting genes involved in IBD). The reference discloses that the level of expression of *c-fos* in the involved IBD samples was about twofold higher than in the uninvolved IBD samples (refers to instant claim 6). Thus, the reference clearly anticipates the claimed invention.

15. Claims 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Dieckgraefe et al (Digestive Disease and Sciences, 114, No.4, G3954, April 1998) (reference provided by applicants in the PTO 1449 filed on 5/16/02).

Dieckgraefe et al disclose a method for identifying gene expressed in IBD. The reference have used GeneChip expression monitoring system to examine mucosal gene expression in ulcerative colitis, Crohns' colitis, and both in inflamed and non-inflamed non IBD specimens. The reference's aim was to identify gene markers differentially expressed in Crohns' disease and ulcerative colitis; identify genotype associated with disease subsets and characteristics. The reference in methods disclose RNA isolated from the mucosa of colonic reaction specimens was used to generate hybridization probes, and light directed solid-phase combinatorial chemistry was used to generate oligonucleotide probe array. The reference in results section discloses that dramatic changes were seen in the expression of wide range of genes, and genes were identified which appear to be specific markers for the specific diagnosis, disease activity and specific feature of histology. Thus, the reference clearly anticipates the claimed invention.

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (Digestive Diseases and Sciences, vol. 41, No. 4, April 1996, pp 660-669) (reference provided by applicants in PTO 1449, filed on 5/16/02).

Alexander et al disclose a method into determine altered expression of protooncogenes (cell cycle related genes) in patients with inflammatory bowel disease (IBD). The reference assayed transcripts of 15 protooncogenes (refer to other IBD genes of the instant claims) in colonic epithelial cells of IBD patients and controls (see abstract). The reference discloses that increased levels of soluble mediators (e.g.. Leukotrienes, prostaglandins) (refer to other IBD genes of the instant claims) of inflammation as well of the cells of immune system have been found to be present in the intestinal mucosa and submucosa of IBD patients (see page 660, last paragraph bridging first paragraph in page 661). The reference discloses expression of transcripts of eight growth factor receptor related genes in colonic epithelial cells of IBD patients and controls (see left column in page 661). The reference discloses that increased expression of PDGF-R-β mRNA involved epithelium, compared to matched uninvolved epithelium, and the

transcript level of this gene, as well three other growth factors was considerably higher in colonic epithelial cells of IBD patients (see page 661).

The reference discloses that prior to determining whether there were any differences between IBD samples and controls in their relative expression of protooncogene transcripts, it was necessary to determine the degree of expression of each of the genes in normal colon epithelial cells (see page 662, right column, section under results). The reference discloses that hybridization of radio labeled probes to slot blots of RNA extracted from normal epithelial cells of patients rejected for diverticulitis and sporadic cancer revealed that transcripts of five protooncogenes were abundant in these samples (refers to a method of selecting genes involved in IBD). The reference discloses that the level of expression of *c-fos* in the involved IBD samples was about twofold higher than in the uninvolved IBD samples (refers to instant claim 6).

The claimed invention differs from the prior art teachings by reciting that the method is used to assess a patients risk of having, or developing an inflammatory bowel disease. The reference discloses a method assaying for protooncogenes in colonic epithelial cells of IBD patients and controls. The reference discloses that the level of expression of *c-fos* in the involved IBD samples was about twofold higher than in the uninvolved IBD samples. Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the method taught by the reference in a method to assess a patients risk of having or developing an inflammatory bowel disease, because the reference teaches a method for comparison of expression of the

specific protooncogenes in IBD patients and controls, and determined that the protooncogenes had a higher expression in the IBD patients compared to the controls.

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner is on ***Increased Flex Schedule*** and can normally be reached on Monday to Friday from 7.00 AM to 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Mckane, can be reached on (703) 308-4537. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

P. Ponnaluri
Patent Examiner
Technology Center 1600
Art Unit 1627
22 July 2002

PADMASHRI PONNALURI
PRIMARY EXAMINER